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10/630,220	07/30/2003	Fabien Marino	IPT-01501	8295

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EXAMINER	
SRIVASTAVA, KAILASH C	

ART UNIT	PAPER NUMBER
1655	

DATE MAILED: 08/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/630,220	MARINO ET AL.	
	Examiner	Art Unit	
	Dr. Kailash C. Srivastava	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-63* is/are pending in the application.

4a) Of the above claim(s) *23-26 and 29-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22,27 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *08/12/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response filed 24 May 2006 to Office Action mailed 22 March 2006 is acknowledged and entered.

2. Applicants' labeling each page of the response referred above with Serial Number of the instant Non-Provisional U.S. Application is greatly appreciated. This practice in and of itself immensely ameliorates the chances of papers lost during transaction/ transmission of paper once a filing/response arrives at the United States Patent and Trademark Office (i.e., USPTO). However, after a response/filing arrives at the USPTO, the claims, remarks, amendments etc., are separated for proper coding to scan them in the electronic file wrapper (i.e., IFW). In order to ensure that all the papers pertaining to a particular application are properly coded and placed in the same application electronic file wrapper, and to further facilitate the prosecution; especially during a telephonic conversation/ interview with applicant/applicants' representative, Examiner suggests that in addition to labeling the header of each and every page of the response with U.S. Non-provisional application Serial Number (i.e., USSN) applicants also recite in the header of the each page for any filing/response/amendment, the following information:

a. Filing date for said application;
b. First Applicant's name;
c. Attorney Docket Number;
d. Group Art Unit Number (e.g., 1655);
e. Examiner's name (e.g., Dr. Kailash C. Srivastava); and
f. Dates of amendment/response as well as the Office Action to which the response is being made.

Papers/responses filed according to above-stated guidelines immensely ameliorate the chances of papers lost during transaction/transmission, coding, indexing and placing the papers in IFW.

Claims Status

3. Claims 1-63 are pending.

Restriction/Election

4. Applicant's election with traverse of Group I, Claims 1-22 and 27-28 filed 24 May 2006 to

Office Action mailed 22 March 2006 is acknowledged and entered. Applicant's traversal is on the grounds that the restriction requirement in Office Action mailed 22 March 2006 is invalid because Examiner has not established "that there is no inventive concept between the claims". Applicants further argue that "the claims of Group I and VI all require a medium for growth of a high density cell Culture" as do claims in Groups VII and IX and therefore, examining of all groups will necessitate the searching of subject matter in Groups I-IX and "not pose an undue burden".

Applicants arguments have been fully and carefully considered, however these arguments are not persuasive for the reasons of record at item 5, pages 3-6 of the Office Action cited *supra* and for the additional reasons discussed *infra*.

Each of the inventions in Groups I-IX are distinguishable from other because they are either drawn to a method having different steps or a composition that does not have same limitations as those in the method claims. Furthermore, the instant application is being prosecuted under 35 U.S.C. §111. Applicants are therefore, reminded that one application one invention rule is applied. In addition, the search for each of the distinct inventions of Groups I-IX is not co-extensive particularly with regard to the literature search because the search strategy for each group requires different considerations than those required for other. In addition, the burden lies not only in the search of U.S. patents, burden also lies in the search

- for scientific and technical non-patent literature;
- foreign patents;
- examination of the claim language; and
- examination of specification for compliance with the statutes concerning new matter, distinctness and scope of enablement.

Clearly different searches and issues are involved with each group. Moreover, a reference that would anticipate the invention of one group would not necessarily anticipate or even make obvious another group. Finally, the condition for patentability is different in each case. For these reasons, the restriction requirement is still deemed proper, is adhered to and is made FINAL.

Applicants are also reminded that Claim 1 links only the claims of groups I-III and VI. Thus, provisions stipulated under the Linking Claim (see Office Action of March 22, 2006, item 4, Page3) is applicable to only those groups.

5. Accordingly, Claims 23-26 and 29-63 are withdrawn from further consideration as being directed to a non-elected invention. See 37 CFR §1.142(b) and MPEP § 821.03. Examiner suggests that the non-elected claims (i.e., Claims 23-26 and 29-63) cited *supra* be canceled in response to this Office action to expedite prosecution.

Priority

6. Applicants' claim for domestic priority under 35 U.S.C.§ 119(e) to 60/399,873, filed 31 July 2002 is acknowledged.

Information Disclosure Statement

7. Applicants' Information Disclosure Statement (i.e., IDS) filed 08 December 2004 is acknowledged, entered and considered.

Claim Objections

8. Claims 1-2, 8-9, 12 and 16-19 are objected to for the following reasons:

- Recitation, "medium" in Claims 1 and 17-19 is ambiguous. Does it mean water, air, a gas other than air, a solid, a liquid other than water or what? The broad interpretation of the term, "medium" is anyone or all of the "matters" exemplified above. Applicants should clearly define the term "medium" (e.g., a culture medium).

- Phrase, "millimoles O_2/liter/minute" in Claims 2 and 9 does not clarify whether the "liter" is related to the flow of oxygen in to the culture vessel or is related to the volume of culture medium.

- Phrase, "substantially maintained" in Claim 8 odes not clarify its significance with respect to temperatures higher or lower than 25°C. Does the phrase, "substantially maintained" relate to the duration of time for which it is maintained at a temperature lower than or higher than 25°C, or is it referring to the temperature range itself. Furthermore, the metes and bounds of temperature higher than or lower than 25°C are not defined.

- Phrase, "cell culture has a volume of less than 200 milliliters" in Claims 12 and 16 is

ambiguous. Applicants are required to clearly define the range for cell culture volume (e.g., 0.00005 mL to 200,000 ml).

- Phrase, "a complex organic material" in Claim 17(ii) is ambiguous because broadly interpreted it can be any matter. Applicants need to clearly state what specific class of material is claimed (e.g., source of organic nitrogen, to be consistent with source of carbon in Claim 17(i)) ?

Appropriate correction is required.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that forms the basis for the rejections under this section made in this Office action:

> ***A person shall be entitled to a patent unless –***
>
> ***(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.***

10. Claims 1, 3-6, 13-15, 22 and 27 are rejected under 35 U.S.C. §102(b) as anticipated by Ye et al. (Journal of Fermentation and Bioengineering, Volume 77, Pages 663-674, 1994).

Claims recite a method to generate a high density cell culture by placing in a culture vessel, wherein said culture vessel is a Tunac-type flask, cells and medium and operating said culture vessel to provide oxygen transfer rate suitable for the growth of a high density cell culture having an optical density at 600 nm (i.e., O.D. $_{600}$) of ≥4. The cells are bacterial cells having a substantial portion thereof comprised of an exogenously regulated expression construct, wherein said construct comprises a lac binding site operably linked to an expressible nucleic acid that is induced with isopropyl-β-D-thiogalactopyranoside (i.e., IPTG). Claims further recite a method to obtain a partially purified polypeptide from said high-density cell culture.

Ye et al. teach a method to produce high-density cell culture by placing in a culture vessel cells and medium and incubating said culture vessel at 37°C with shaking at 110 rpm (Page 664,Column 2, Lines 4-13 below Table 2). Under those conditions, a high-density cell culture having an optical density at 600 nm (i.e., O.D. $_{600}$) of ≥4 is obtained. Said high cell density is obtained by growing a recombinant *Escherichia coli* to a cell yield on the basis of dry cell weight of at least 84 g/l of culture medium (Abstract Lines 4-6). Said cultivation (See Page,

663, Column 2, Lines 27-46) is carried out in a culture vessel (i.e., T-shaped flask), wherein growth of said *Escherichia coli* containing a lac operon construct is regulated by an external inducer- isopropyl-β-D-thiogalactopyranoside (i.e., IPTG). From said high-density cell culture of *Escherichia coli,* a partially purified β-galactosidase is obtained through toluene-mediated lysis of cells (Page 665, Column 1, Lines 27-37). Note that the T-shaped flask is similar to a "Tunac-type" flask, the cells are bacterial cells and since Ye et al. teach that an $O.D._{600}$ of 1 for *Escherichia coli* grown under the conditions of cultivation described in Ye et al. is equivalent to 0.45 gram of dry cell weight l^{-1} (Page 665, Column 1, Lines 18-26), 84 g of dry cell weight l^{-1} (Abstract, Line 6) is = an $^{O.D.600}$ of 186.7. Furthermore, said *Escherichia coli* cell also comprises a lac-linked site, wherein expression of a polypeptide linked to said site is controlled by an exogenous inducer, i.e., IPTG. In absence of applicant's clear recitation of how much of the construct is in the bacterium they claim comprises a lac binding site operably linked to an expressible nucleic acid that is induced with IPTG and produces a high density cell culture; Ye et al also teach a bacterium comprising a lac binding site nucleic acid expressed with an exogenous inducer, said inducer being IPTG. Since applicants recite a partially purified polypeptide, without defining the number of amino acid residues in said polypeptide and Ye et al. teach that their active β-galactosidase is obtained by lysing the cells with toluene, Ye et al. also teach a partially purified polypeptide obtained from a high density cell culture.

Thus, the reference teaches a method that appears to be identical to all the steps and components claimed in the instantly claimed method.

Therefore, the cited reference is deemed to anticipate the claims cited *supra.*

Claim Rejections - 35 USC § 102/103

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that forms the basis for the rejections under this section made in this Office action:

> ***A person shall be entitled to a patent unless –***
>
> ***(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.***

12. The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> ***(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the***

time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § ***102***(f) or (g) prior art under 35 U.S.C.§ 103(a).

14. Claims 1-7, 9-22 and 27-28 are rejected under 35 U.S.C. §102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Ye et al. (Journal of Fermentation and Bioengineering, Volume 77, Pages 663-674, 1994).

Claims recite a method to generate a high density cell culture by placing in a culture vessel, wherein said culture vessel is a Tunac-type flask or a 96 well plate, cells and medium and operating said culture vessel to provide oxygen transfer rate > 2.0 mM O_2/l. min^{-1}, the growth of a high density cell culture having an optical density at 600 nm (i.e., $O.D._{600}$) of ≥4. The cells are bacterial cells having a substantial portion thereof comprised of an exogenously regulated expression construct, wherein said construct comprises a lac binding site operably linked to an expressible nucleic acid that is induced with isopropyl-β-D-thiogalactopyranoside (i.e., IPTG). Claims further recite a method to obtain a partially purified polypeptide from said high-density cell culture. Additionally the culture medium is comprised of:

i. a carbon source selected from glucose or glycerol (glycerol concentration of 0.5-5%);
ii. an organic nitrogen among: beef broth, hydrolyzed casein, tryptone (tryptone at a concentration of 10-14 /l) and yeast extract (yeast extract at a concentration 20-30 grams/l)
iii. a source of magnesium at a concentration of 0.5 to 2 mM;
iv. two or more metals among: aluminum, boron, calcium, cobalt, copper, iron, manganese, molybdenum, nickel, and zinc; and
v. buffering salts comprising potassium phosphate at a concentration of 100 and 200 mM and pH of 6-8.

Ye et al. teach a method to produce high-density cell culture by placing in a culture vessel cells and medium and incubating said culture vessel at 37°C with shaking at 110 rpm (Page 664,Column 2, Lines 4-13 below Table 2). Under those conditions, a high-density cell

culture having an optical density at 600 nm (i.e., O.D. $_{600}$) of ≥4 is obtained. Said high cell density is obtained by growing a recombinant *Escherichia coli* to a cell yield on the basis of dry cell weight of at least 84 g/l of culture medium (Abstract Lines 4-6). Said cultivation (See Page, 663, Column 2, Lines 27-46) is carried out in a culture vessel (i.e., T-shaped flask), wherein growth of said *Escherichia coli* containing a lac operon construct is regulated by an external inducer- isopropyl-β-D-thiogalactopyranoside (i.e., IPTG). From said high-density cell culture of *Escherichia coli,* a partially purified β-galactosidase is obtained through toluene-mediated lysis of cells (Page 665, Column 1, Lines 27-37). Ye et al. further teach a medium composition comprising similar or same ingredients (e.g., glucose 10g is within the rang of 0.5-5%/l) as instantly claimed. Note that the T-shaped flask is similar to a "Tunac-type" flask, the cells are bacterial cells and since Ye et al. teach that an O.D.$_{600}$ of 1 for *Escherichia coli* grown under the conditions of cultivation described in Ye et al. is equivalent to 0.45 gram of dry cell weight l^{-1} (Page 665, Column 1, Lines 18-26), 84 g of dry cell weight l^{-1} (Abstract, Line 6) is = an $^{O.D.600}$ of 186.7. Furthermore, said *Escherichia coli* cell also comprises a lac-linked site, wherein expression of a polypeptide linked to said site is controlled by an exogenous inducer, i.e., IPTG. In absence of applicant's clear recitation of how much of the construct is in the bacterium they claim comprises a lac binding site operably linked to an expressible nucleic acid that is induced with IPTG and produces a high density cell culture; Ye et al also teach a bacterium comprising a lac binding site nucleic acid expressed with an exogenous inducer, said inducer being IPTG. Since applicants recite a partially purified polypeptide, without defining the number of amino acid residues in said polypeptide and Ye et al. teach that their active β-galactosidase is obtained by lysing the cells with toluene, Ye et al. also teach a partially purified polypeptide obtained from a high density cell culture.

Thus, the reference teaches a method that appears to be identical to all the steps and components claimed in the instantly claimed method.

However, even if the reference and the claimed method are not one and the same and there is, in fact, no anticipation, the reference method would, nevertheless, have rendered the claimed method obvious to one of ordinary skill in the art at the time the claimed invention was made in view of the fact that the reference teaches all of the components and steps and even the culture vessel as that recited in the claims. Applicants have admitted on record that the vessel is anyone among: fermenter vessel, Tuanc flask or 96 well microtiter plate or other vessel (See instant application specification, Page 14, Lines 7-14) and medium is a minimal

medium comprising a source for carbon (e.g., glucose), a nitrogen source (e.g., NH4Cl) and sources for calcium, chloride, magnesium, phosphorus, potassium, sodium and sulfur (See instant application specification page 13, Lines 14-19). The prior art reference does not teach the same exact concentration of components in the minimal medium as instantly recited. However, the adjustment of particular conventional working conditions (e.g., interchangeable conditions of temperature, pressure, pH, oxygen concentration, different components of a culture medium and quantities thereof) is deemed merely a matter of judicious selection and routine optimization of a result-effective parameter, which is well within the purview of the skilled artisan.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

Thus the claimed invention as a whole was clearly *prima facie* obvious especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> ***(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.***

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § *102*(f) or (g) prior art under 35 U.S.C.§ 103(a).

17. Claims 1--22 and 27-28 are rejected under 35 U.S.C. §103(a) as obvious over the combined teachings from Ye et al. (Journal of Fermentation and Bioengineering, Volume 77,

Pages 663-674, 1994) in view of Caldwell et al (Bioseparation, Volume 6, Pages 115-123, 1996).

Claims recite a method to generate a high density cell culture by placing in a culture vessel, wherein said culture vessel is a Tunac-type flask or a 96 well plate, cells and medium and operating said culture vessel to provide oxygen transfer rate > 2.0 mM O_2/l. min^{-1}, the growth of a high density cell culture having an optical density at 600 nm (i.e., O.D. $_{600}$) of ≥4. The cells are bacterial cells having a substantial portion thereof comprised of an exogenously regulated expression construct, wherein said construct comprises a lac binding site operably linked to an expressible nucleic acid that is induced with isopropyl-β-D-thiogalactopyranoside (i.e., IPTG). Claims further recite a method to obtain a partially purified polypeptide from said high density cell culture, wherein during the culture temperature is maintained higher or lower than 25°C during growth and induction phases respectively. Additionally the culture medium is comprised of:

i. a carbon source selected from glucose or glycerol (glycerol concentration of 0.5-5%);
ii. an organic nitrogen among: beef broth, hydrolyzed casein, tryptone (tryptone at a concentration of 10-14 /l) and yeast extract (yeast extract at a concentration 20-30 grams/l)
iii. a source of magnesium at a concentration of 0.5 to 2 mM;
iv. two or more metals among: aluminum, boron, calcium, cobalt, copper, iron, manganese, molybdenum, nickel, and zinc; and
v. buffering salts comprising potassium phosphate at a concentration of 100 and 200 mM and pH of 6-8.

Ye et al's teachings discussed *supra*, do not explicitly teach that pH was maintained in the range of 6-8 and that the temperature was varied during the growth and induction phases.

Campbell et al. teach that cultivation of a recombinant *Escherichia coli* to express and produce a recombinant protein was conducted in a culture medium comprising tryptone, yeast extract, potassium phosphate and glycerol (Page 115, Column 1, Lines 15-28) maintained at a pH of between 6-8-7.1 (Page 115, Column 1, Lines47-48), wherein the organism was cultivated at 30°C and after the induction the temperature was first raised to 40°C then reduced to 20°C and held at 4°C until the fermentation broth was further processed (Page 115, Column 1, Lines 45-51; Page 115, Column 2, Lines 1-4)

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings from Ye et al. with those from Campbell et al., because as discussed *supra*, Ye et al. teach cultivating in a T-shaped flask a high density cell culture of a recombinant *Escherichia coli* having a lac fragment that expresses itself \with an exogenous inducer- IGPT, wherein said recombinant *Escherichia. coli* is cultivated at 37 C in a medium comprising similar carbon nitrogen magnesium and other micronutrient sources as instantly claimed and further teach obtaining a partial purified polypeptide; and Campbell et al. teach purifying a polypeptide obtained from a high density cell culture of a recombinant *Escherichia coli,* wherein said culture is cultivated in a culture medium having same composition, maintained at a pH range of 6.8-7.1 and further at a temperature of 30°C during cultivation and at a temperature of 20°C and 4°C after induction. The prior art reference does not teach the same exact concentration of components in the minimal medium as instantly recited. However, the adjustment of particular conventional working conditions (e.g., interchangeable conditions of temperature, pressure, pH, oxygen concentration, different components of a culture medium and quantities thereof) is deemed merely a matter of judicious selection and routine optimization of a result-effective parameter, which is well within the purview of the skilled artisan.

One having ordinary skill in the art at the time of the claimed invention would have been motivated to modify/combine the teachings from Ye et al. with those from Campbell et al., because as discussed *supra* Ye et al. teach a method to prepare a high density cell culture of a recombinant *Escherichia coli* possessing a lac binding site operably linked to an exogenous inducer- IPTG to produce a recombinant polypeptide, wherein said polypeptide is expressed, recovered and partially purified from said high density culture and Campbell et al teach cultivating a high density recombinant *Escherichia coli* to express, produce and purify a recombinant protein, wherein said *Escherichia coli* is cultivated in a medium comprising the same ingredients as instantly claimed and further said recombinant *Escherichia coli* is cultivated at a pH in range of 6.8-7.1 and a temperature of 30°C and after induction the temperature is maintained first at 20°C and then at 4°C.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at

the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

18. The prior art made of record and not relied upon is considered pertinent to Applicants' disclosure.

- Anderson et al., U.S. PGPB 20050181979. Printed 18 August 2005; and
- Sabbadini et al., U.S. PGPB 20030190601. Printed 9 October 2003.

Claim Rejections - 35 U.S.C. § 112

19. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> ***The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.***

20. Claims 1 and 28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled that the inventor(s), at the time the application was filed, had possession of the claimed invention. From the record of the present written disclosure, the scope of the claimed invention recited in claims 1 and 28 taken together is not supported by the specification on record.

The specification as currently presented while describing the cultivation of a recombinant cell placed with a medium in a flask, beaker or other type of vessel to generate a high density culture having an Optical Density at 600 nm (i.e., $O.D._{600}$) of greater than 4, despite stating that any or all culture vessels are interchangeable, does not explicitly describe how an $O.D._{600}$ of greater than 4 is obtained when the claimed organism is cultivated in a 96 well plate.

A person of skill would not be able to practice the claimed invention in a 96-well plate due to the quantity of experimentation necessary; limited amount of guidance and limited number of working examples in the specification; nature of the invention; state of the prior art; relative skill level of those in the art; predictability or unpredictability in the art; and breadth of the claims. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Undue experimentation will

be necessary because there is no recited guidance, example or teaching in the specification to obtain the instantly claimed high density cell culture of a bacterium in any one of the wells of a 96 well plate.

21. Claims 1 and 28 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with those claims. Claims are directed to a "method to generate a high density cell culture by placing a medium and cells in a culture vessel" and "operating said culture vessel" to provide a oxygen transfer rate to grow a high density cell culture, wherein said high density culture has an $O.D._{600}$ of greater than 4. Said culture vessel is a 96-well plate.

From the record of the presently filed written disclosure, the specification only demonstrates the cultivation of a recombinant cell placed with a medium in a flask, beaker or other type of vessel to generate a high density culture having an Optical Density at 600 nm (i.e., $O.D._{600}$) of greater than 4. IN said disclosure, despite describing that any or all culture vessels are interchangeable, there is no explicit description about how an $O.D._{600}$ of greater than 4 is obtained when the claimed method is carried out in a 96 well plate. Thus, the claimed invention is not considered commensurate in scope with those claims because one of ordinary skill will not be able to make and/or use the invention.

A person of skill would not be able to practice the claimed invention to obtain a high density cell culture in each or any well of a 96-well plate due to the quantity of experimentation necessary; limited amount of guidance and limited number of working examples in the specification; nature of the invention; state of the prior art; relative skill level of those in the art; predictability or unpredictability in the art; and breadth of the claims. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Undue experimentation will be necessary because there is no recited guidance, example or teaching in the specification to obtain the instantly claimed high density cell culture of a bacterium in any one or all of the wells of a 96 well plate.

22. The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> ***The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.***

23. Claims 1-22 and 27-28 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

- Phrase "high density cell culture" in Claims 1 and 22 renders that Claim vague and indefinite because the metes and bounds for the phrase, "high density" is not defined in those claims. Appropriate correction/definition is required.

- The phrase, "cell culture" in Claims 1, 5, 7-8, 12, 14, 16, and 22 renders those claims unclear and vague because of the definition given for the phrase "cell culture" in the specification. While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The phrase, "Cell culture" in claims 1, 5, 7-8, 12, 14, 16, and 22 has been used to mean a viable and growing cell in it's culture medium" which is the art-accepted meaning for a "Cell culture" (see for e.g. Singleton and Sainsbury, Dictionary of Microbiology and Molecular Biology, Page 565, Column 2, Line 30). The metes and bound for the phrase, "cell culture" should be clearly established.

- Recitation, "suitable" in claims 1 and 9 is unclear and indefinite. It is not clear how one can determine with clarity and accuracy when a certain condition or set of condition is suitable and what may be suitable for one may not be suitable for another. Applicants should define the meted and bounds for the term "suitable".

- Despite the definition given in the specification for the phrase, " simple culture vessel", said renders claims 1, 9 and 11 unclear, vague and indefinite. The metes and bounds for the phrase, "simple culture vessel" should be defined.

- Recitation, "substantial" or "substantially" in claims 4 and 8 renders those claims unclear, vague and indefinite because the metes and bounds for the term "substantial" or "substantially" are not defined. In either the specification or the claim and an artisan of skill will not be able to appreciate the claimed invention as currently presented.

- Abbreviation, "IPTG" at line 3 renders Claim 6 unclear, vague and therefore indefinite. Abbreviations in the first instance of claims should be expanded upon with the abbreviation indicated in parentheses. The abbreviations can be used thereafter. Appropriate correction is required.

- In Claim 7 at Line 2, the phrase, "when culture has an OD_{600} of 1 or greater" lacks sufficient antecedent basis because Claim 7 depends from Claim 5, which depends from Claim 1. IN claim the limitation is,"OD_{600} of 4 or greater". Appropriate correction is required.

- Claim 8 is rejected because of the range within range, i.e. broad limitation followed by a narrow limitation. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation in the same claim is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in Ex parte Wu, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of Ex parte Steigewald, 131 USPQ 74 (Bd. App. 1961); Ex parte Hall, 83 USPQ 38 (Bd. App. 1948); and Ex parte Hasche, 86 USPQ 481 (Bd. App. 1949). In the present instance, "temperature higher than 25°C" followed by "temperature lower than 25°C", are construed as broad and narrow.

- In Claim 12, the limitation of "cell culture has a volume of less than 200 milliliters" lacks sufficient antecedent basis. This is because Claim 12 depends from Claim 11, which depends from Claim 1. The preamble for Claim 12 does not state that the limitation "cell culture has a volume of less than 200 milliliters" is additional to that given in Claim 11 or in Claim 1 and in any one of claims 11 or 1 there is no limitation of culture volume. Appropriate correction is required.

- In Claim 14, the limitation of "cell culture has a volume of between 500 and 2000 milliliters" lacks sufficient antecedent basis. This is because Claim 14 depends from Claim 13, which depends from Claim 1. The preamble for Claim 14 does not state that the limitation "cell culture has a volume of between 500 and 2000 milliliters" is additional to that given in Claim 13 or in Claim 1 and in any one of claims 13 or 1 there is no limitation of culture volume. Appropriate correction is required.

- In Claim 16, the limitation of "cell culture has a volume of less than 200 milliliters" lacks sufficient antecedent basis. This is because Claim 16 depends from Claim 15, which depends from Claim 1. The preamble for Claim 16 does not state that the limitation "cell culture has a volume of less than 200 milliliters" is additional to that given in Claim 15 or in Claim 1 and in any one of claims 15 or 1 there is no limitation of culture volume. Appropriate correction is required.

Conclusion

24. For reasons aforementioned, no Claims are allowed.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kailash C. Srivastava whose telephone number is (571) 272-0923. The examiner can normally be reached on Monday to Thursday from 7:30 A.M. to 6:00 P.M. (Eastern Standard or Daylight Savings Time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Terry McKelvey, can be reached on (571)-272-0775 Monday through Friday 8:30 A.M. to 5:00 P.M. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding may be obtained from the Patent Application Information Retrieval (i.e., PAIR) system. Status information for the published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (i.e., EBC) at: (866)-217-9197 (toll-free). Alternatively, status inquiries should be directed to the receptionist whose telephone number is (703) 308-0196.

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